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Re: **Docket No. 2005D-0062**; Draft Guidance for Industry on the Food and Drug Administration's "Drug Watch" for Emerging Drug Safety Information (Federal Register 24606 – 24607, Vol. 70, No. 89, Tuesday, May 10, 2005, Notices)

Dear Sir/Madam:

The following comments on the above-referenced draft guidance document on Drug Watch are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures and markets leading prescription medicines for humans and animals and many of the world's best-known consumer health care brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier and more productive lives. The company has three business segments: human health care, animal health care and consumer health care. Our products are available in more than 150 countries.

Health is our top priority at Pfizer, so we support any initiatives that improve the safe use of medicines. We believe that the dissemination of appropriate, understandable information about drugs is good for the public health; we want people, in consultation with their physicians, to make appropriate decisions about taking medicines and whether to stay on prescribed regimens; we want people to be able to benefit from modern medicines by understanding fully their potential therapeutic value and the risks they necessarily bring. Pfizer believes Drug Watch has the potential to serve the public's need in this regard – if done carefully.

We also believe that it is important that FDA make this effort toward increased communication more explicit in order to assuage public fears about the safety of its drug supply. Pfizer believes that FDA has for years faithfully and successfully executed the mandate of Congress to monitor and protect the safety of medicines. FDA's initiative to launch a high profile Drug Watch list may provide FDA the opportunity to let the public know what FDA currently does and what it has done for years. It is also an opportunity for the FDA to educate the public that all drugs have risks as well as benefits, just like

every activity in our daily lives, and that taking drugs requires tradeoffs. Conveying that message is very much in the public's interest.

Throughout the detailed comments to follow are some high level principles to which Pfizer believes FDA should adhere in order to optimize the public health benefit of Drug Watch, while minimizing its potential to do just the opposite. They may appear obvious, but they are so fundamental they bear repeating in the context of this new program.

First – and foremost – it is incumbent on FDA to be vigilant in protecting individuals, not just the safety of their drug supply. Safety includes honoring the sovereignty of individuals in making well-informed choices about whether or not to take a medicine, and their rights to have an unencumbered personal relationship with a physician to assist them in that task. In all matters related to Drug Watch, FDA must retain uncompromising attention to how elements of this new program will affect individual choices. FDA must be ever mindful that the person reading the web page is not an "average patient," but an individual with unique personal circumstances, varying capacity to comprehend, closely held beliefs and preferences, and the personal right to act as he or she sees fit on neutral, unbiased information. The population must never be mistaken for the individual; to add value, and to make drug use safer, Drug Watch must always defer to the individual.

Second, FDA must be mindful that it lacks the authority to mandate to doctors how they should practice medicine. The complex art of medicine in the context of biodiversity demands science, not conjecture. The diversity of our genes guarantees that people will react to drugs differently. Selection of therapeutic options should be made only within the bounds of the patient-physician relationship where that diversity is best known, and no proclamation on the Drug Watch web site should ever bias the critical decision-making that takes place within that relationship. Drug Watch should stick to facts – not speculate.

Third, since Drug Watch is meant to make drug use safer, it is important that there be clarity and precision regarding drug safety. In the questions and answers addendum to the draft guidance on Drug Watch, the response to Question 7 states: "FDA makes decisions about the safety of a particular drug after considering its benefits to treat a particular condition in relations to its risks. FDA therefore considers a drug safe when its benefits outweigh its risks for its intended use." This statement underscores a vitally important point: drug safety is not defined by potential or real risks; only the balance of risks within the context of benefits defines it. This principle should be an overarching theme of Drug Watch. Every communication to the public through Drug Watch should contain this balance of risk and benefit information, reminding of the benefits of the drug (its approved uses) as well as what may be its potential or emerging risk. Otherwise, patients may be unnecessarily frightened from taking needed medicines, the physician-patient relationship will be interfered with, the rights of the individual will be compromised, and Drug Watch will not improve drug safety.

These overarching principles guide Pfizer's assessment of the Drug Watch guidance. We have identified three major areas that deserve close attention in order for Drug Watch to

achieve its goal of safer drug use. Detailed comments are attached to this letter; here are brief, summary comments regarding each of those areas:

Processes

All stakeholders need to know how Drug Watch will work, how decisions will be made to post and withdraw drugs from the site under what time frames, where do the emerging risk data come from, who is to be held accountable, what are the website's checks and balances, etc. The success of Drug Watch will depend to a great extent on the degree to which the public trusts the FDA in protecting their interests through this endeavor. The processes must be well defined, explicit and inclusive, and the public must be assured that their concerns are met. Pfizer believes strongly that public confidence in Drug Watch also will be proportional to the involvement in the process by the practicing physician. Practicing physicians, not administrators or academics, should be given major responsibilities as consultants to FDA, especially on matters related to analysis and communication.

Pfizer further notes that omission of industry, as consultant to this process, is counter-productive if not dangerous. Since the stated goal of Drug Watch is to protect the public health by warning it about emerging or potential safety issues, it is prudent to use all possible resources available to the FDA, including those resources with the greatest possible insight and knowledge about a specific medicine. FDA should ensure an inclusionary process by inviting sponsors to fully participate in the Drug Watch initiative.

Analyses

In order to interpret Drug Watch information, patients, physicians, pharmacists and industry all need to know how and why a drug will be chosen for inclusion on the web site, and how and when it will be removed. The analysis of selection and de-selection of products for posting should be made explicit and vetted with the public. Included in this exposition should be a detailed explanation of the data and the evaluation techniques to be used: what will trigger a listing; what safety information will be used in the system; what are the safeguards that will be used to identify spurious data; etc.

Since data on adverse events come from a variety of sources with varying degrees of reliability, FDA should use data in its analyses that have been weighted according to reliability. When FDA reports to the public the sources of data for a Drug Watch listing, it should provide a link to another web page describing the reliability and importance FDA ascribes to the data it has used in its analyses. This issue has even more importance when FDA considers adverse event reports from nations with less sophisticated regulatory and pharmacovigilance standards.

Pfizer also recommends that FDA build evaluation measures into Drug Watch to determine how well the "emerging safety issue" communication system is actually working; for example, what is the percentage of false positives on the Drug Watch list and what has been the impact on the public. We also reiterate that since drug sponsors are in a position to know more than any other entity about their drugs, it is in the public's interest to have FDA consult with sponsors about emerging safety issues.

Communications

In developing this communication vehicle, the goal of informing the public of emerging risk information must be balanced with the need to avoid causing needless alarm. In an effort to provide the most up-to-date information on emerging data, specious inferences may be drawn and medicines may be falsely branded as "risky." This could unnecessarily alarm and confuse doctors and patients, discourage patients from taking needed medicines, and detract attention from the benefits of the medication and the risks of not taking it. It is important that physicians and consumers not focus on the absolute risk of a drug, but instead consider its benefit-risk balance and its relative risk compared to other drugs, and the underlying condition if left untreated. For each medicine on the Drug Watch web site, FDA should remind the public of its benefits as well as what might be its potential or emerging risks.

FDA needs to ensure that information communicated on the Drug Watch web site is clear and understandable. Literature on communicating risk to the public indicates that many persons are innumerate and cannot understand some of the basic mathematics used in risk concepts. FDA should use a panel of experts to identify a range of communication formats to optimize comprehension of its Drug Watch information over as broad a spectrum of the population as possible.

Pfizer strongly agrees with the Agency's stance that the listing of a drug on Drug Watch must not to be taken as an opportunity for a competitor manufacturer whose similar drug is not on Drug Watch to improve the marketing of its drug. FDA should enhance its vigilance on false advertising and promotion, implicit or explicit, and bring to bear against violators of this rule the full weight and force of its office. The rule should be stated emphatically in each listing of Drug Watch.

The substance of the above remarks reiterate Pfizer's strong commitment to the safe use of medicines, and endorsement of the underlying goal of FDA's initiative to improve risk communication to the public. We believe that Drug Watch, if correctly implemented, may represent an opportunity both to improve safety and to strengthen trust among the public. This initiative is very ambitious and it must be crafted carefully since it will be complex to implement in such a way that more people use drugs appropriately.

We thank FDA for the opportunity to comment on this draft guidance, and are pleased to respond to any questions the Agency may have about our comments.

Sincerely,

Gretchen S. Dieck

Gretchen S. Dieck

Detailed Comments

Processes

The processes that FDA opts to employ for communicating emerging risk information to the public are critically important for patients, caregivers and healthcare practitioners. Because the information posted on Drug Watch could have significant ramifications for patient health and safety, it is imperative that any standards and processes FDA adopts to implement Drug Watch be clear, consistent and well defined. Accordingly, we offer the following comments regarding suggested improvements in the processes set forth in the draft Guidance for Drug Watch:

Sponsor Involvement in the Decision to Post its Drug on Drug Watch

Pfizer believes that it is critical that a Sponsor be integrally involved in both the decision to post one of its drugs on Drug Watch and the specific language to be used in the posting. We fully recognize that the Agency wants to act quickly to disseminate information to healthcare providers and patients. However, because a Sponsor has the most knowledge about its products and the data for those products, Sponsors have an essential role to play regarding the dissemination of information regarding that product.

FDA correctly notes (footnote 4) that it regularly discusses information with Sponsors about the side effects of their drugs. To have and expect such discussions, but to then decline to provide Sponsors with the opportunity to play a role in an initiative such as Drug Watch, may serve to undercut the open exchange of information that FDA expects from regulated industry and may ultimately serve to deny doctors and consumers the best possible information about a posted product.

Sponsor Pre-Review of the Drug Watch Posting

Sponsor pre-review of the proposed FDA Drug Watch posting must also be addressed. Such review will be essential in helping to ensure that information posted on the website is accurate, thereby minimizing the posting of erroneous information. If FDA posts information in error, the ramifications for patients and prescribers can be significant - patients may stop taking medications on the basis of erroneous or incorrect information, prescribers may decide to cease prescribing the posted drug and/or tell their patients to stop taking the drug in question. Substantial damage to the public health, and to the public's confidence in Drug Watch, may occur if information is incorrectly posted. That damage might be impossible to undo with, e.g., a "corrective" posting, as it would be impossible for the Agency to ensure that such corrective posting would reach all of the consumers and prescribers who read and relied upon the erroneous information on the website. Accordingly, Pfizer requests that FDA explicitly provide for Sponsor pre-review of the posting.

Notification to and Involvement of the Sponsor

FDA must establish a process by which the Sponsor will be drawn into the discussion of the alleged safety issue. It is important for Sponsors to have full and timely access to the underlying information upon which FDA is considering posting so that they can evaluate that information, bring their own resources to bear upon it, and be ready to assist the FDA's on-going analysis, as appropriate.

To that end, the Guidance should specifically provide a Sponsor notification process that will include, among other things, provision of a copy of all information being considered by FDA, the source of the information, and any special analyses performed by FDA with respect to the issue.

Sponsors must be consulted at the time FDA is conducting its preliminary analysis, and given a defined period of time to provide any additional information that may help to clarify the potential safety concern. Sponsors' contributions could include such things as new adverse event reports or analyses that are still in the processing cycle, exposure information, or other perspectives that may contribute to an understanding of or resolution of the concern. This additional Sponsor perspective, if any, should be made available during the initial decision-making process, i.e., when the Drug Safety Oversight Board (DSOB) is considering the topic of concern. Further, FDA should give due consideration to any additional information about a drug provided by the Sponsors at any time during the period a drug is on Drug Watch to ensure that FDA uses all of the resources at its disposal and the most timely information is provided on Drug Watch.

The draft Guidance states that Sponsors will be notified "shortly before" the first instance in which information regarding their product is posted on the Drug Watch Web site (lines 216-218). As stated above, FDA needs to involve the Sponsor in the decision to post and the content of the posting, not just to "notify" it "shortly before" the posting.

Appealing the Decision to Post a Drug on Drug Watch

The Draft Guidance does not provide any process by which a Sponsor may appeal FDA's decision to post its drug on Drug Watch, nor does the Draft Guidance provide a process by which a Sponsor may propose alternative wording for the site posting. Critical to the integrity of the process is the establishment of a mechanism enabling the Sponsor to request DSOB review, and withdrawal or rewording of the posted information. Such appeal would, of course, need to be based upon definitive, established criteria that could demonstrate that the posting was inaccurate or otherwise lacking a credible basis.

Linking a Product Drug Watch Posting to the Product Prescribing Information

As discussed elsewhere in these comments, Pfizer believes it is essential that any Drug Watch posting contain not only information about emerging "risks" for a drug product, but also the known benefits of the product. Only where benefits and risks are linked can healthcare prescribers and consumers obtain the full information about the product and

make informed decisions about the appropriate course of action for a given patient in light of the "emerging" information. Accordingly, each posting on Drug Watch should also contain a link to the drug product label. The product label is, and must remain, the most definitive source of information about a drug product.

Creation of a Process for Updating the Website

In the draft Guidance, FDA states that it intends to work "as quickly as possible to assess and address the potential safety issues..." (lines 37-38), and that it intends to update information on the Drug Watch frequently (lines 130-131). The Guidance should include the establishment of a process regarding the nature and frequency of the updating process, including minimum cycle times for updating the site, the procedures to be used to resolve an issue, and the establishment of an "archive" that demonstrates the evolution of emerging information for each posted product over time.

In addition, we suggest that the Drug Watch posting include information regarding the steps the Agency is taking to assess and address each emerging safety issue, and the estimated timeframe for completion of this assessment. In the interest of the public health, the single entity with the most knowledge about a given drug, the drug's Sponsor, should be included in all proceedings on updating and removal of products from the site. There should be a specific mechanism established by a which a Sponsor, or other entity, can request an update to the web site based on the receipt of further information or further evaluation of the issue.

In some instances, FDA's further evaluation of emerging safety information may find a causal relationship between a drug and an adverse event and may identify information that could have an impact on the prescribing of a drug (e.g., the identified adverse event affects only a specific patient population). In such cases, the confirmed risk information should be incorporated into the drug's label; information posted on Drug Watch should not supplant the information contained in the drug label. FDA should ensure that the Drug Watch posting is updated to reflect regulatory action (e.g., drug label is changed).

The Draft Guidance must set forth the processes by which the Website will be updated, particularly where a purported safety issue has been "resolved," including a determination that no causal relationship has been found. Documenting resolution of a posted issue is an important aspect of the process that will reassure the public that issues have been adequately addressed. This in turn will help to instill greater confidence in the program. Therefore, it is important that a product be removed from the Drug Watch in a timely manner and the rationale for its removal be provided on the website. Information regarding product removal from the site should be accorded the same level of highlighting and publicity that the original posting received. Information regarding the product removal should remain on the web site for a period of time that is sufficient to assuage public fears about the drug, perhaps 12 months. We also recommend that the Agency develop and maintain a permanent on-line reference for each issue that is posted to the Drug Watch, including how it was evaluated, and its resolution.

The Drug Safety Oversight Board

In lines 173-203, FDA sets forth the representation of the Drug Safety Oversight Board ("DSOB"). The Board contains representatives from CDER, CBER, CDRH, and other Department of Health and Human Services Offices. The draft Guidance also permits the DSOB to consult with the FDA Advisory Committee Chairs, other external scientific experts and consumer and patient representatives. Conspicuously absent from the list is any form of industry representation.

We believe it is critical that FDA formally include regulated industry on the list of *potential* consultants to the DSOB. Because the pharmaceutical industry, in general, and drug Sponsors, in particular, have extensive knowledge about the products they market and the diseases they treat, it is important that industry be recognized as a potentially valuable resource for the DSOB. To decline to permit industry participation in the process would ultimately serve to undercut Drug Watch by eliminating a critical source of extensive information about the product, disease state, epidemiologic information etc. This would not be consistent with FDA's avowed purpose of providing the public with access to "the most up-to-date and emerging product information ..." (lines 60-61).

Establishing a Process for Initial and On-Going Analysis of Physician And Patient Response to Drug Watch

It is critical that, prior to launching Drug Watch, FDA develop a process to determine:

a. The most effective means of communicating emerging safety information to physicians and consumers from both a content and format perspective; and

b. How physicians and consumers will likely respond to emerging safety information posted on the website.

Because Drug Watch represents a radical departure from prior Agency policy, i.e., providing *emerging* safety information to the public, FDA must proceed in a measured and considered way and assess how best to communicate such information to optimize public response. (See Section below re: Communicating Risks). It is important that FDA understand how the public is likely to respond to information posted on Drug Watch before launching this new policy. FDA should revise and refine the Drug Watch program on the basis of the findings of these analyses.

Analyses

Background

FDA states: "Our goal with the Drug Watch is to share emerging safety information before we have fully determined its significance or taken final regulatory action so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug product upon which to make individual treatment decisions" (lines 64-68). In other sections of our response to this Drug Watch draft guidance we have noted that reporting unsubstantiated, "emerging" safety issues to the public has the potential to do harm as well as good, harm arising when patients are unnecessarily frightened away from taking needed medicines. How FDA defines terms, selects data and uses analyses both for listing and de-listing is integral to ensuring a beneficial process while avoiding harm.

Defining and Using Terms Appropriately

If FDA is still analyzing information while posting it, not yet having reached a conclusion about a drug's safety, we do not think it realistic to expect that patients or even healthcare providers will be able to make proper sense of the situation either. This is particularly acute for most patients who are likely not to have understanding of pharmacology of medicines. It is critical, therefore, for FDA to clearly define what it means by "a significant emerging safety issue."

We recommend that FDA be cautious in its use of the term "signal" to represent an emerging safety issue, as in: "... when FDA has determined that, despite the initial signals, there is no new safety concern" (lines 211-212). A handful of adverse events reports do not constitute a "signal;" it could be background noise. The use of the term could confuse people, since most of the public will not know what a "signal" is in the context of drug safety. Use of the term "signal" on Drug Watch also would be a false representation of what is being posted. Until a drug-injury event is confirmed, it would be safer for the public to call data posted on Drug Watch "reports."

The Drug Watch guidance states that Drug Watch will provide information about drugs with "significant" emerging safety issues (line 76), but other parts of the document (lines 33, 34, 35, 64, 65, 93, 94, 120-124) indicate that the aim of the program is in part to determine if emerging safety concerns are, in fact, significant at all. The ultimate aim of Drug Watch is to determine whether an emerging issue posted on Drug Watch is statistically or medically significant; the significance of an emerging issue is not known at the time of posting. Hence, the term "significant" can be confusing in this context and we recommend that it not be used where an issue may be "emerging."

Terms that will be used in analyses, both preliminary and follow-up, should be clearly defined so they are usable and understandable by all stakeholders. We suggest further guidance on Drug Watch clarify what is meant by terms describing analyses, such as "emerging" (line 19), "actively evaluating" and "early" (line 22), "causal relationship"

(line 86), "adverse events" (line 87), and "risk/benefit assessment" (line 88). We strongly recommend that terms be defined clearly in a well-written glossary, with a link to it on each posting on the Drug Watch website. We suggest links to a glossary (as well as links to descriptions of data and analytical techniques) in order to both better inform stakeholders seeking such information and avoid overwhelming and confusing users who have more limited capacities to comprehend Drug Watch information and messages.

The Drug Watch Disclaimer

Pfizer believes the proposed FDA disclaimer is insufficient: "This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this web page when additional information or analyses become available" (lines 121-124). We suggest the disclaimer be expanded to include a statement saying that neither a scientific association or a causal relationship has been established, and the validity of the information is subject to verification, but that rather in an abundance of caution this information is being shared. The statement should also include the fact that sometimes these emerging reports do not lead to any risk finding. Further, the disclaimer should specifically state that the information is not yet considered sufficient to warrant a change in the product's prescribing information (its label). We recommend FDA precede this information with direct communications to patients about discussing their use of the drug with their doctor (described in detail in the following section on communications) so that they may consider the patient's particular circumstances, and what the benefits and risks of the medication might be for that patient.

Criteria for Posting on Drug Watch

There are discrepancies throughout the Drug Watch draft guidance with respect to the nature of the safety issues FDA intends to address on Drug Watch and the standards FDA intends to apply in determining whether to post a product on the site. The criteria for posting information on the Drug Watch must be more explicitly defined. This is particularly important because the information will be posted "before (FDA) has fully determined its significance" (line 65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers, patients, and other regulators, it is crucial to have clearly defined parameters for the selection of products and information to be posted.

The first listed criterion, "Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored" (lines 153-157) is vague with regard to the strength of the information necessary to make such a determination (e.g. number of cases needed and robustness of reports). We recommend the guidance also specify the criteria used in determining that "an unapproved (off-label) use of the drug appears to pose a significant risk to patients" (lines 162-163). FDA should further clarify how products with widespread off-label usage fit into this category.

It is unclear whether the Drug Watch postings will be limited to only emerging safety issues that would be considered "serious" pursuant to 21 C.F.R. §314.80 or whether "non-serious adverse events" could be subject to posting. This issue requires clarification.

FDA notes (lines 167-168) that before posting information on Drug Watch, the Agency will conduct a "...preliminary analysis to determine that the new safety information is sufficiently credible..." Absent from the draft Guidance, however, is any indication as to what might constitute a "preliminary analysis" and what thresholds or criteria would be deemed to be "sufficiently credible." This issue also requires clarification.

The confusion in standards and definitional criteria is evidenced in the examples of potential postings FDA provides in the draft Guidance. There is an inconsistency between the general inclusion criteria for Drug Watch, i.e., "emerging safety information," and the examples provided in this section (lines 83-110), particularly examples B and C. These examples discuss risks for which conclusions appear to have been established, not which are "emerging."

Risk management action plans (example C), or RiskMAPs, especially do not belong on Drug Watch. RiskMAPS are used in cases where the drug-injury event is well specified (and not "emerging"), and FDA and the Sponsor has decided on a course of action to manage risks. Because the information supporting RiskMAPs is so well developed, posting a RiskMAP on Drug Watch - a list meant to describe unsubstantiated safety issues – would only serve to diminish the RiskMAP's impact.

FDA should vet with the public transparent analysis plans that detail the events to be included and the methodologies that will be used to select those events for posting. Detail should be sufficient to allow the patients, non-healthcare professionals and healthcare providers the ability to use the information appropriately if they so wish. After posting a drug, FDA should make careful use of the best available "data mining" techniques and other analytic paradigms in order to rapidly uncover real "signals" or identify false ones.

Weighting Evidence

In addition to concerns regarding the lack of specificity on the standards, discussed above, Pfizer believes that is essential that FDA be explicit about the strength of the information necessary to make a determination to post. Absent from the draft Guidance is any reference, for example, to the number of reports or data sources necessary to trigger inclusion on Drug Watch and/or the robustness of the reports. Certainly reports from treating physicians should be accorded more weight and "validity" than anecdotal reports from non-treating healthcare professionals or sales representatives from competitor companies. Lawsuits themselves are often adverse drug event reports, and these should be afforded very little weight. The FDA Guidance Document must provide detail regarding its intended approach to the weighting of the evidence to ensure consistency and transparency in the analytical process.